matter. In particular, claim 2 of the originally filed specification defines GDF-1 by the amino acid sequences of Figures 2, 11A or 11B.

Claims 3, 11-15 and 22-23 are pending in this application; claim 23 has been withdrawn from consideration by the Examiner as drawn to a non-elected invention.

Applicant acknowledges with appreciation the interviews with the Examiner and her supervisor Donald Adams on October 15, 1996, and Richard Schwartz, Biotechnology Practice Specialist, on December 16, 1996.

Claims 3, 11-15 and 22 were rejected under 35 U.S.C. 112, first paragraph, as allegedly "not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention". Applicant traverses.

On page 2, lines 21-23 of the Office Action (Paper No. 31), it is alleged that the claimed invention is not enabled because "there is no evidence of record that this DNA sequence encodes a biologically useful protein possessing any particular properties". Applicant submits that this is not the proper standard for patentability under Section 112, first paragraph, as the biological function of a protein is only one potential use for the claimed invention.

The specification states on page 12, lines 20-23, "one potential use for GDF-1 as a diagnostic tool is as a specific marker for the presence of tumors arising from cell types that normally express GDF-1". The skilled artisan would understand that this can be generalized to the use of GDF-1 as a lineage marker for normal tissues as well (see temporal- and tissue-specific expression of GDF-1 discussed on pages 23-24 of the specification).

Figure 6 shows a 1.4 kb transcript was detected in embryos of 8.5 and 9.5 days gestation, but not in later stage embryos. A second RNA species of 3.0 kb appeared at day 9.5 and persisted throughout embryogenesis. Thus, the size of the GDF-1 transcript could be used to determine a cell's embryonic stage and would be valuable in determining the action of growth and differentiation factors on the developing embryo or in cell culture.

Figure 7 shows that in adult tissues, GDF-1 was expressed almost exclusively in the brain, although GDF-1 was also detected in the adrenal gland, ovary, and oviduct. Thus, in addition to use of GDF-1 as a marker for a cell's stage of embryonic development, restriction of GDF-1 expression to particular adult tissues would be valuable in determining the tissue of origin for a cell.

Detection of GDF-1 expression is not limited to Northern blot analysis. The specification describes the generation of

specific antibodies to GDF-1 protein and their use in Western blot analysis (see Example 5 on pages 24-25 of the specification). The skilled artisan would recognize that such techniques are known in the art (page 12, lines 3-7 of the specification), and that detection of protein to determine temporal- or tissue-specific expression of GDF-1 would be an alternative to detection of RNA. Thus, GDF-1 protein, nucleic acids encoding the GDF-1 protein, and methods of producing GDF-1 protein would be useful in developing antibody to GDF-1.

A rejection based on an alleged lack of enablement requires that evidence, or a reason, be provided by the Examiner to substantiate an assertion that the objective truth contained in the disclosure is doubted. M.P.E.P. 2164.01. This burden of persuasion has been described by the Court:

> "[I]t is incumbent on the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure."

In re Marzocchi, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971).

As shown by citation to the present specification and the understanding that a skilled artisan would gain from reading that specification, the claimed invention would find use in determining a cell's stage of development and/or its tissue of origin. Such determination would find application in any

situation in which a mixture of cell types is suspected. For example, determining whether a tumor arose from a cell of the surrounding tissue (i.e., a primary tumor) or was a metastasis from a different tissue would have diagnostic and treatment consequences. For cultures of undifferentiated cells, the action of growth or differentiation factors on the culture may be determined by detection of GDF-1. For determining the developmental stage of an embryo, determination of GDF-1 would provide a marker of age.

As discussed above, the use of antibody binding to GDF-1 protein provides an art-recognized alternative to nucleic acid hybridization. Such an antibody would be generated using GDF-1 protein, preferably produced recombinantly, as described in the specification.

If this rejection is maintained and in accordance with In re Marzocchi, the Examiner is requested to provide evidence or a reason to substantiate doubting the objective truth that GDF-1 transcript and/or protein would be useful in determining the lineage of a cell, or that such a determination would not have "practical utility".

On pages 3-4 of the Office Action (Paper No. 31), it is alleged that "the method of claim 15 is not sufficiently described or enabled" as the recombinant production of GDF-1 protein (e.g., Figure 9) is not presented in sufficient detail to determine what was performed. Applicant submits that the

detailed description of Figure 9 is irrelevant to teaching how to make and use the invention of claim 15. The specification describes the DNA and protein sequences of GDF-1, and it would not require undue experimentation to produce the protein recombinantly given the disclosed sequences. The technical details of Figure 9 are irrelevant to the patentability of the claimed invention under Section 112, first paragraph, because the claimed invention is not, and should not be, limited to the example of protein fusions described in Figure 9.

The Examiner asserts, "It would constitute undue experimentation to determine how to use the claimed invention in the manner set forth in the specification" (page 4, lines 3-5 of Paper No. 31). As discussed above, the claimed invention is not, and should not be, limited to Figure 9 and, therefore, a detailed experimental protocol is not relevant to enablement of claim 15. The specification states on page 11, lines 32-35, "The recombinant DNA molecule of the invention can be introduced into appropriate host cells by one skilled in the art using methods well known in the art". The Examiner has not indicated that such methods were not well known in the art, and applicant submits that disclosure of the DNA and protein sequences of GDF-1 is what would be required for the skilled artisan to practice the invention of claim 15.

If this rejection is maintained, the Examiner is requested to explain with particularity the nature of the

"undue experimentation" that would be required to produce recombinant GDF-1 protein given the disclosure of its DNA and protein sequence in the specification.

Claims 3, 11-15 and 22 were rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite. Applicant traverses and submits that Figure 2, 11A and 11B clearly show an amino acid sequence which is GDF-1.

For the above reasons, applicant requests withdrawal of the objections to the specification and the rejections of the claims under Section 112.

Having fully responded to the Office Action dated December 10, 1996, a Notice of Allowance is requested. The Examiner should contact the undersigned if further information is needed.

Respectfully submitted,

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